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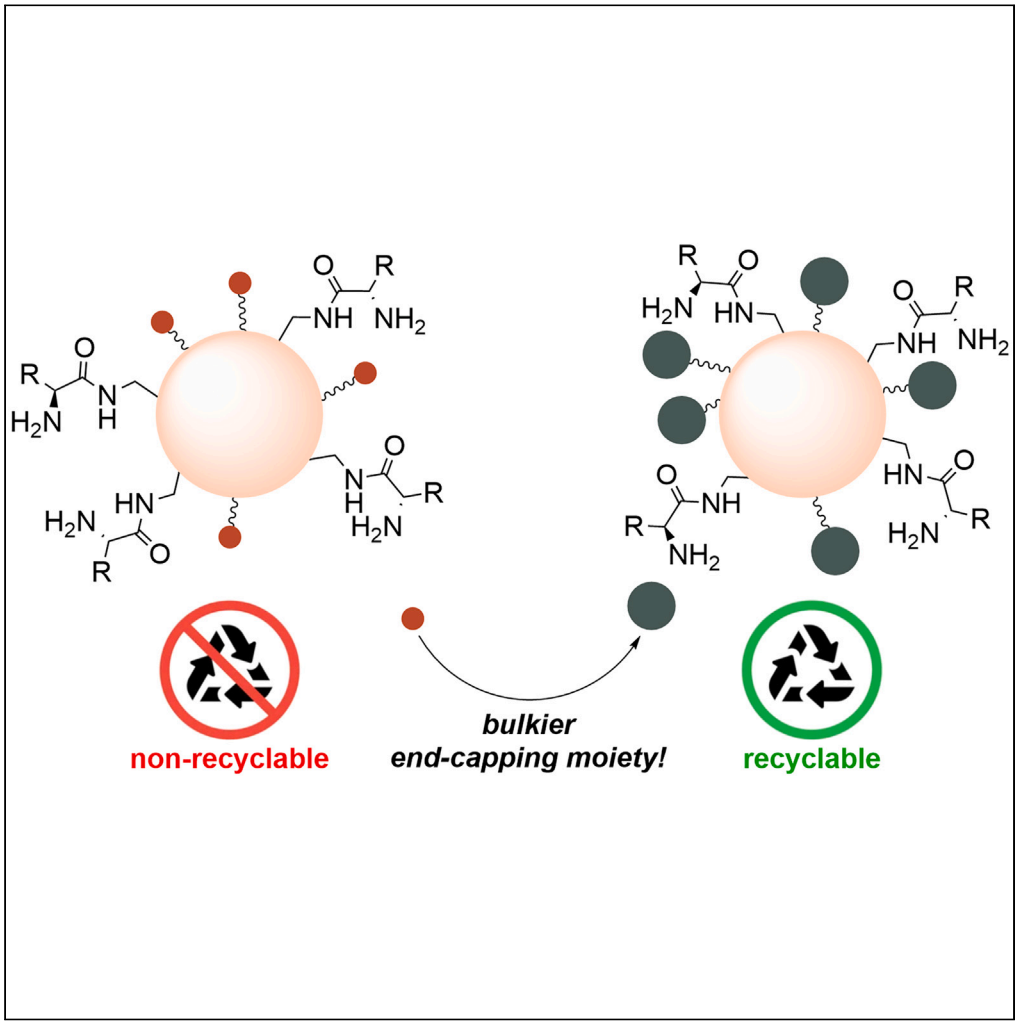

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Highlights

Chiral heterogeneous primary amino acid-derived catalysts were synthesized

Challenges related to the reusability of the catalytic system were resolved

The essential role of end-capping was showed as pivotal for achieving recyclability

Pivaloyl chloride was the most efficient reagent for the end-capping

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Primary amines as heterogeneous catalysts in an enantioselective [2,3]-Wittig rearrangement reaction

Aleksandra Murre,[1] Valdek Mikli,[2] Kristin Erkman,[1] and Tõnis Kanger[1,3,*]

SUMMARY

A series of heterogeneous catalysts anchored to different polystyrene-based supports has been prepared and applied in an asymmetric [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives. Among them, primary amino acid-derived (aminomethylated)polystyrene-supported catalysts showed excellent reactivity leading to the formation of rearranged products in good enantioselectivities of both diastereomers. Reusability issues connected to the deactivation of the catalyst were proved to be dependent on the end-capping strategy chosen for the blocking of the unreacted active sites of the resin. This issue of end-capping has not previously been in focus. Using bulkier pivaloyl end-capping moiety, we were able to recycle the catalyst in six consecutive cycles with only marginal deceleration of the reaction. Moreover, the epimerization of the product that occurred while conducting a rearrangement reaction in the presence of a homogeneous catalyst was almost fully eliminated by switching the catalytic system to heterogeneous.

INTRODUCTION

As sustainability becomes a viral concern, it creates challenges for constant improvement. Solutions to the problems connected with using large amounts of catalyst and the production of enormous quantities of waste must be found.[1,2] Heterogeneous catalysis provides a versatile opportunity to meet this goal.[3–5] The main benefit of using catalysts immobilized on solid support is the simplified isolation of the desired chiral product and convenient catalyst recovery using just a filtration/washing sequence.[6] Consequently, this makes the reaction setup less complex and, therefore, makes it possible to consider these reactions for manufacturing processes.[7–10] Since the pioneering work of the immobilization of proline onto a polymer support,[11] the field of the incorporation of chiral aminocatalysts on solid supports has begun to develop fast. Many examples are available for the successful use of both soluble and insoluble polymer-supported iminium-activation-based catalysts, especially prolines, imidazolidinones and their derivatives in different types of catalytic reactions.[12–16] However, the incorporation of chiral primary amines onto solid supports and their implementation as asymmetric catalysts are rather limited.[17–20] In addition, challenges associated with the reusability of the polymer-supported primary aminocatalysts sometimes arise, thereby narrowing their merits and application possibilities. The current study provides a deep insight into appeared recyclability issues and solutions for their elimination.

New carbon-carbon bond formation has always been one of the biggest challenges for organic chemists. Many synthetically useful reactions have been successfully developed and optimized to extend the carbon framework.[21] Well-known 100%-atom efficient rearrangement reactions are among the major tools used for this purpose.[22] A [2,3]-Wittig rearrangement reaction is a base-induced new C-C bond forming reaction occurring simultaneously with the breakage of a C-O bond (Scheme 1A).[23,24] In the case of ketones or aldehydes used as an electron-withdrawing group (EWG), a [2,3]-Wittig rearrangement reaction can also be promoted by enamine catalysis via increasing the nucleophilicity of the α-position of the EWG (Scheme 1B).[25]

Here, we introduce a successful and robust pathway for synthesis of cheap, easily accessible, and recyclable polystyrene-supported primary amines as catalysts and their application in the asymmetric [2,3]-Wittig rearrangement of cyclohexanone derivatives as an example of an efficient method for the synthesis of enantiomerically enriched homoallyl alcohols bearing two consecutive stereocenters.

RESULTS AND DISCUSSION

We have recently reported an asymmetric [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives.[26] Utilizing a structurally simple primary amine, substituted α-hydroxyketones were obtained with high yields, diastereoselectivities and enantioselectivities of the major diastereomer (Scheme 2). However, this approach is not devoid of limitations, since the epimerization of the rearrangement product happened

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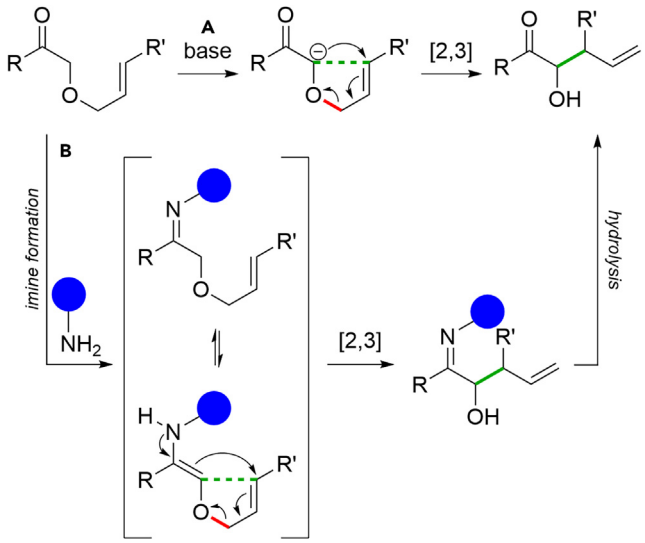


Scheme 1. [2,3]-Wittig rearrangement reaction promoted by base (A) or enamine catalysis (B)

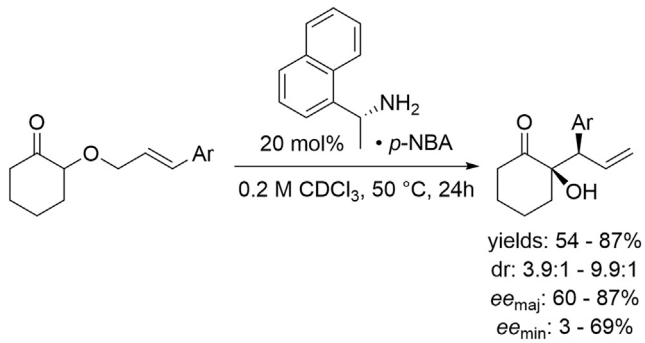
under the [2,3]-Wittig rearrangement conditions, diminishing enantioselectivity, especially drastically for the minor diastereomer. Additionally, high catalyst loading (20 mol %) is required for this reaction to be effective. Bearing in mind those problems and challenges, we decided to study whether a heterogeneous catalysis would help to overcome the limitations.

At the onset of the project, we considered different immobilization strategies of primary amines onto the divinylbenzene cross-linked polystyrene resins (Scheme 3, color codes were used throughout the article to differentiate solid supports). The incorporation of the organocatalysts onto the resin was easily followed by IR spectrometry and the loading of immobilized catalysts was estimated by the nitrogen content obtained from elemental analysis.

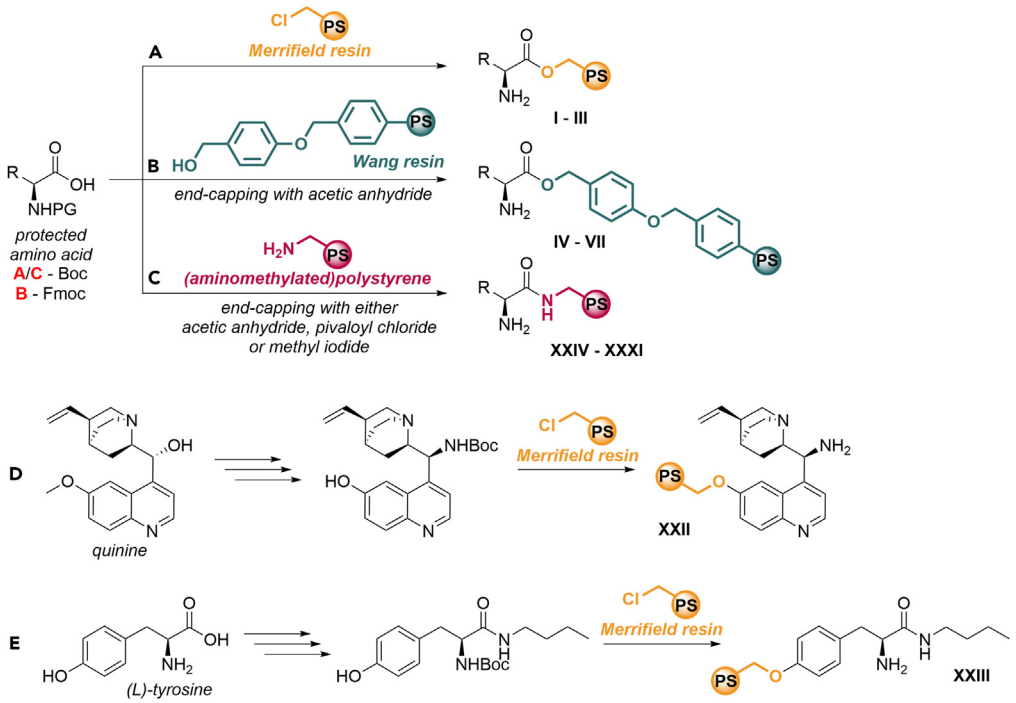
Firstly, a Merrifield resin was functionalized with protected α-amino acids in the presence of potassium fluoride. After the deprotection step catalysts **I–III** were obtained with 0.59–0.64 mmol/g loading range (Scheme 3A). To explore the effect of the linker length, the hydroxybenzotriazole (HOBt)/*N*,*N*′-diisopropylcarbodiimide (DIC)-catalyzed condensation of protected amino acids with a Wang resin was also used. It should be noted that, as the incorporation of organic molecules onto the resin is usually not full, functional groups of the resin may remain unreacted. Depending on the type of functionality, different blocking strategies are used to provide completely inert support.[27] Therefore, unreacted active sites of the resin were end-capped with acetic anhydride. Then, the protecting group of the amino acid part was removed yielding the formation of the ester-linked supported catalysts **IV–VII** (Scheme 3B).

In addition, a Boc-protected bulkier quinine derivative and tyrosine derivative were directly attached to the Merrifield resin via a nucleophilic substitution reaction in the presence of sodium hydride and potassium iodide, forming an ether bond, followed by the deprotection step. According to elemental analysis, the catalysts **XXII** and **XXIII** were isolated with loadings of 0.6 mmol/g and 0.34 mmol/g, respectively (Schemes 3D and 3E).

Finally, different protected α-amino acids were coupled with the (aminomethylated)polystyrene using peptide synthesis conditions. The remaining free primary amines of the resin were blocked using 3 different techniques; the reaction with acetic anhydride or pivaloyl chloride led to the formation of amides, and methyl iodide was used to prepare an alkylated resin. Removing the protecting group of the amino acid moiety provided the catalysts **XXIV–XXXI** with moderate loadings in the range of 0.38 mmol/g–0.59 mmol/g (Scheme 3C).[28]



Scheme 2. [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives; *p*-NBA – para-nitrobenzoic acid



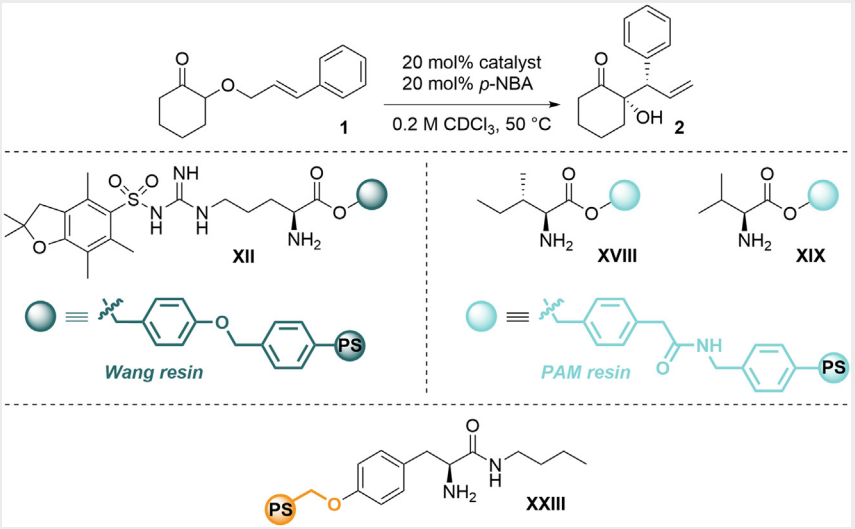
Scheme 3. Immobilization strategies of primary amines used in this work HOBt – hydroxybenzotriazole; DIC – N,N′-diisopropylcarbodiimide; DMAP – 4-dimethylaminopyridine

We started the investigation of the [2,3]-Wittig rearrangement of cyclohexanone derivatives under previously optimized reaction conditions for homogeneous catalysis with immobilized catalysts connected with the resin by an ester bond.[26] Reactions were carried out in $CDCl_3$ in the presence of a corresponding immobilized catalyst and a catalytic amount of *para*-nitrobenzoic acid (*p*-NBA). The reaction mixture was shaken in a temperature-controlled shaker at 50°C. The initial screening of the catalysts is represented in the supplementary information, Table S1. In this study, the series of both self-made (**I–VII**) and commercially available (**VIII–XXI**) catalysts (structures are available in supplementary information, Table S1) bonded to the Merrifield, Wang or *p*-hydoxymethylphenylacetamidomethyl polystyrene (PAM) resins through an ester moiety were tested showing sluggish catalytic efficiency. Even though, in some cases, full conversion was obtained, enantioselectivity remained low (up to 46%, See supplementary information, Table S1, entries 1–21). More importantly, our study revealed a major problem associated with the reusability of this type of catalysts, as already the second cycle of the recycling led to a diminished conversion and *ee*-s of the product (Table 1, entries 1–3).

Alternatively, a catalytic reaction was also conducted in toluene and acetonitrile. However, in both cases, the catalysts were still not recyclable (Table 1, entries 4–5). The possible leakage of the amino acid moiety from the resin was eliminated by elemental analysis, as the functionalization level (according to the nitrogen content) of the initial and recycled catalysts was nearly identical. To ascertain whether some structural changes in the catalyst happened during the rearrangement reaction, the IR spectra of reused catalysts were measured. This showed the appearance of an additional carbonyl band, suggesting intramolecular amidation of primary amine by the ester groups. It can happen either between primary amines of the catalysts and ester bonds formed during the end-capping of the corresponding catalysts with acetic anhydride or between two different units of amino acids bounded to the polymer matrix, not necessarily involving the end-capped ester moiety. Both scenarios led to the inactivation of the supported catalysts (Figure 1).

To prevent undesired blockage of the catalytic site, catalysts attached to the resin via an ether bond were used. Surprisingly, the catalyst **XXII**, made from a bulkier alkaloid, gave almost no reaction at all (See supplementary information, Table S1, entry 22). The tyrosine derivative **XXIII** showed moderate reactivity with very good enantioselectivity (88% for both major and minor diastereomers; See supplementary information, Table S1, entry 23). Unfortunately, the attempt to recycle the catalyst **XXIII** was unsuccessful (Table 1, entry 6). In the case of the catalyst **XXIII**, primary amines can be potentially alkylated by remaining unreacted chloride moieties on the resin (presence of the chlorine was confirmed by SEM), and that is why end-capping with NaOMe was conducted. However, this did not improve the reusability of the catalyst as a significant drop in both reactivity and selectivity was detected. As an elemental analysis and IR spectroscopy did not provide an explanation for such behavior, an additional morphological analysis was conducted. The mechanical degradation of the support material may also have been responsible for the shortening of the lifespan of the catalysts on the resin,[29–31] and this is why scanning electron microscopy (SEM) images of the initial (Figure 2A) and deactivated catalysts (Figure 2B) were obtained. SEM investigation was made with the help of Zeiss Field Emission Gun – Scanning Electron Microscope (FEG-SEM) Ultra-55. In Figure 2 high resolution mode at 4 kV accelerating voltage (AV) and In-lens SE detector was used. SEM images revealed no breakage of the polymer. Both catalysts appeared to be surface-wrinkled. The particle

Table 1. Recycling experiments for the [2,3]-Wittig rearrangement reaction of 1 with catalysts XII, XVIII, XIX, and XXIII



	Catalyst	I Cycle	Conv,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]	II Cycle	Conv,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]
1	XII		96	4.4:1	21	35		48	4.1:1	5	7
2	XVIII		78	2.9:1	39	38		15	2.7:1	23	19
3	XIX		62	2.9:1	46	46		5	ND	ND	
4[d]	XIX		58	3.3:1	58	56		16	2.6:1	14	8
5[e]	XIX		46	3.3:1	58	62		16	2.6:1	8	8
6	XXIII		44	3.5:1	88	88		12	3:1	44	50

p-NBA, *para*-nitrobenzoic acid; nd, not determined.

Reaction conditions: 0.1 mmol scale, solvent (0.5 mL). The major diastereomer is depicted in the scheme.

[a]The conversion was determined after 22 h by ^{1}H NMR of the crude reaction mixture.

[b]The diastereomeric ratio was determined by ^{1}H NMR of the crude product.

[c]The enantiomeric excess was determined by a chiral high-performance liquid chromatography (HPLC) analysis of the sample obtained by preparative thin-layer chromatography (TLC).

[d]Toluene was used instead of $CDCl_3$.

[e]ACN was used instead of $CDCl_3$.

size is significantly smaller in deactivated catalyst (Figure 2A, scale 20 μm; Figure 2B, scale 10 μm) and their shape is a little irregular in the borders. This indicates a change in the matrix inner structure that can cause an impact in reaction outgoing.

As the tyrosine derivative **XXIII** gave rise to enantioselectivity of the desired product, we envisioned a cooperative effect between the amide proton and primary amine. Thus, we turned our attention to re-designing the immobilized catalysts. Consequently, series of catalysts **XXIV–XXVIIIa** attached through the carboxylic acid to the (aminomethylated)polystyrene were prepared (Scheme 3C).

Gratifyingly, the catalysts **XXIV–XXVIIIa** exhibited excellent catalytic performances with notable increase in the enantioselectivities (Table 2). The performance of immobilized organocatalysts was not significantly dependent on the side chain of the used amino acids, affecting mostly the diastereoselectivity of the obtained product.

As mentioned previously, the main advantage of heterogeneous catalysis is reusability. Thus, our next step was to explore the recyclability of the catalysts on the (aminomethylated)polystyrene. Unfortunately, the activity of both tested catalysts **XXVII** and **XXVIIIa** decreased drastically in the second cycle, leading to the diminished conversion of the reaction and the enantioselectivities of the rearrangement product. However, at the same time, this did not affect the diastereoselectivity (Table 3, entries 1 and 2). Next, the effect of the solvent nature and influence of the temperature on the performance of the reaction and, most importantly, on the reusability of the catalyst was studied (Table 3, entries 3–6). The obtained results revealed that catalysts recycled from the reactions performed in toluene or acetonitrile could still not be reused as significant drop in both reactivity and enantioselectivity was observed. However, even though the conversion of the reaction decreased by lowering the temperature, the recycled catalyst showed a smaller drop in reactivity. This observation suggested that structural changes in the catalyst by intramolecular side-reactions were decelerated at lower temperature. In order to explain this behavior, the IR spectra of the recycled catalysts were measured. The appearance of an additional band at the carbonyl region on the IR spectrum was detected, which correlates with the hypothesis of an intramolecular *trans*-amidation reaction happening between the primary amino groups of

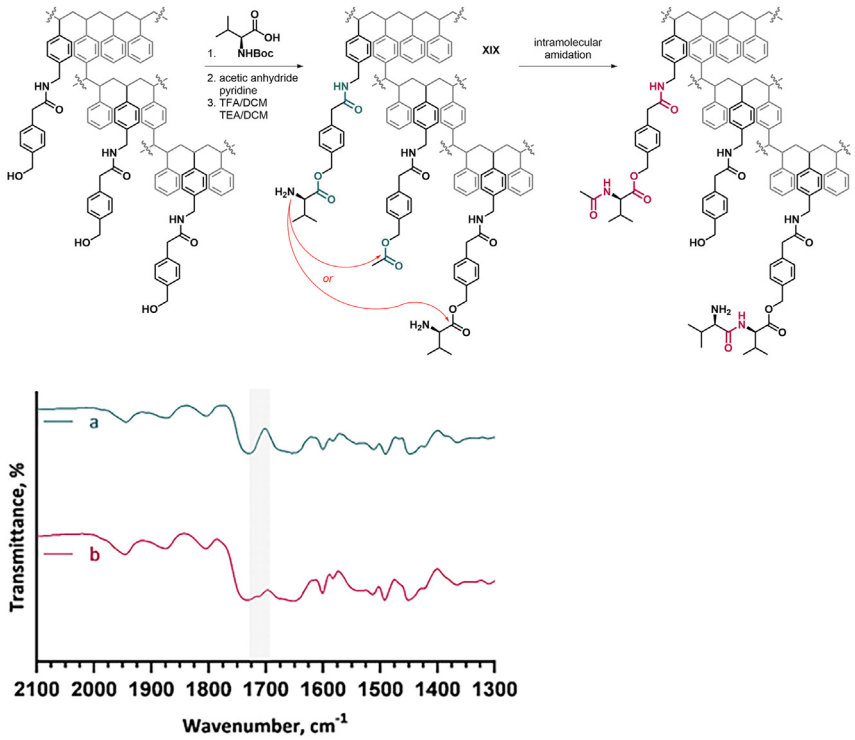


Figure 1. Deactivation of catalyst

(A and B) Plausible deactivation mechanism on the example of catalyst XIX and IR spectra of initial (A) and reused (B) catalyst **XIX**.

the catalyst and the end-capped amides of the resin under the [2,3]-Wittig rearrangement conditions. In an attempt to circumvent this drawback, two different end-capping methods were tested (Scheme 4).

In the catalyst **XXVIIIb**, the unreacted primary amines of the resin were end-capped with methyl iodide, yielding alkylated amines instead. Even though the catalyst performance in the second cycle was better than with the catalyst **XXVIIIa** (Table 3, entries 1 and 7), drop in both conversion and enantioselectivities was still observed. A solution to this problem was found using bulkier pivaloyl chloride for the end-capping of the unreacted primary amines on the resin, which provided the catalyst **XXVIIIc**. To our delight, the catalyst **XXVIIIc** showed the same reactivity as well as selectivities as the previously tested catalysts **XXVIIIa** and **XXVIIIb** in the first cycle, with remaining productivity in the second cycle (Table 3, entry 8).

Considering these findings, the catalysts **XXIX**–**XXXI** were additionally synthesized, following the same procedure as in the case of the catalyst **XXVIIIc**, utilizing the end-capping strategy with pivaloyl chloride. Of these, the catalysts **XXVIIIc** and **XXIX** showed the best catalytic performance, yielding rearrangement product **2** in full conversion with high enantiopurity (Table 4, entries 1 and 2). Notably, the catalyst **XXX**, with close structural similarity to the catalyst **XXIX**, led to the formation of product with disappointingly low enantioselectivities of both major and minor diastereomers (Table 4, entry 3). Such an outcome can be explained by the partial racemization of the catalyst. Due to the increased acidity of the benzylic α-proton of the phenylglycine, it is prone to racemize under the peptide synthesis conditions used to implement amino acid residue with the resin.[32] Surprisingly, a bulkier *tert*-butyl group at the α-position (the catalyst **XXXI**) did not improve the enantioselectivities of the product and, moreover, significantly decreased the diastereoselectivity (Table 4, entry 4). As additional optimization experiments using different solvents, temperature and amount of catalyst conducted with the catalyst **XXIX** did not show improvements in the reaction outcome, we proceeded with standard reaction conditions (See supplementary information, Table S2).

Once the catalysts with the higher catalytic performance (the catalysts **XXVIIIc** and **XXIX**) had been established, their robustness was tested with the recycling experiments (Figure 3; for detailed information see supplementary information, Table S3). After 22 h, an immobilized catalyst was separated from the reaction mixture by filtration, washed successively with chloroform and methanol, and dried. Then, the next experiment was carried out by the addition of a fresh batch of reagents and solvent to a sample of the recycled catalyst. The catalyst **XXVIIIc** was successfully reused four times without any loss in reactivity, affording product with constant diastereo- and enantioselectivities. However, surprisingly, a rapid drop in the activity of the mentioned catalyst was detected starting with the fifth cycle, also leading to a decrease in selectivities. We were pleased to find that the catalyst **XXIX** showed even better recyclability, leading to excellent catalytic performance in six consecutive cycles with only marginal erosion of conversion and enantioselectivities. The decrease in conversion became more significant in the seventh cycle and it continued to drop further after that (seventh cycle: 71% conversion after 16 h, eighth cycle: 48% conversion after 16 h); remarkably, however, there was no influence on the selectivities of the rearrangement product.

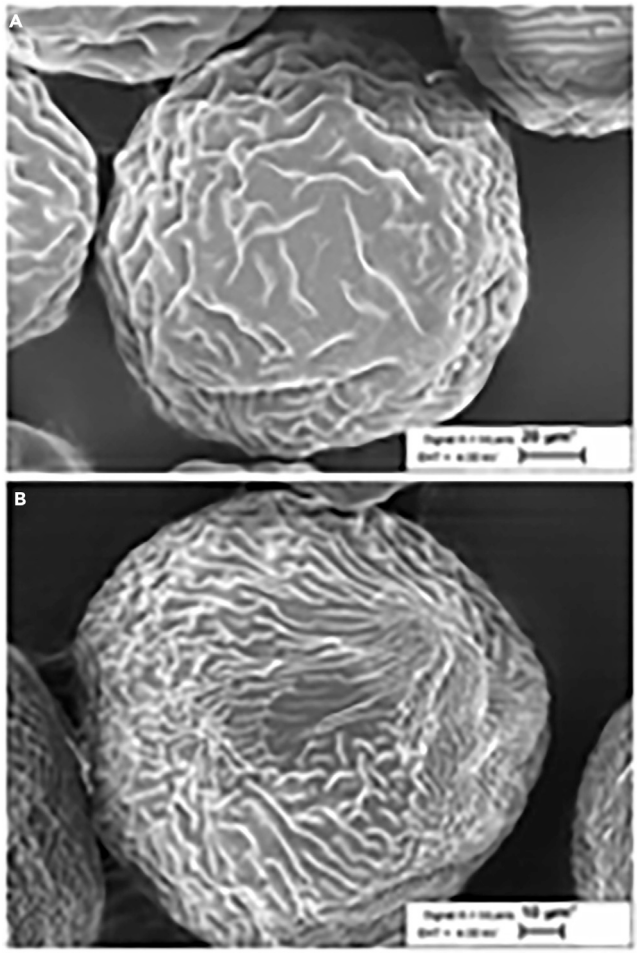


Figure 2. SEM images
(A and B) SEM images of initial (A) and deactivated (B) catalyst **XXIII**.

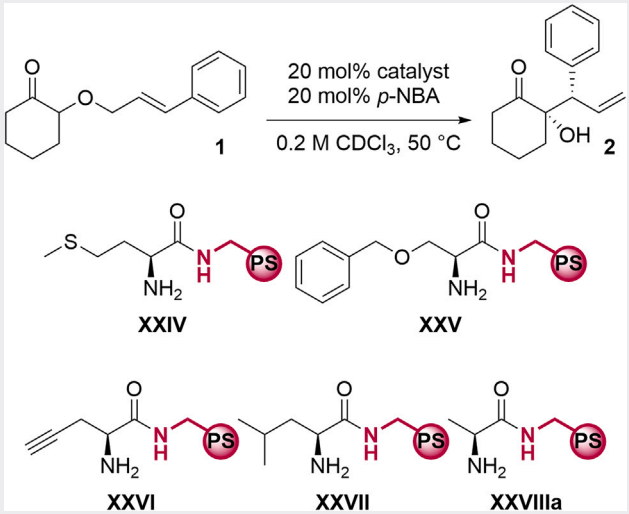
In order to elucidate the degradation of the catalyst, the IR was measured for the reused catalysts **XXVIIIc** and **XXIX** (Figure 4). As previously, the appearance of an additional carbonyl band on the IR spectra was noticed. However, only in the case of the reused catalysts **XXVIIIc** and **XXIX** did a peak at 2,245 cm^{-1} emerge. A plausible explanation for this is CO_2-induced carbamate formation from primary amine, ultimately resulting in catalyst deactivation.[33] The catalyst **XXIX** was also characterized by SEM using conventional Back-scattered imaging mode at 15 kV AV (Figure 5). We did not observe any substantial changes in the catalyst morphology.

While conducting the [2,3]-Wittig rearrangement reaction in the presence of a homogeneous catalyst, a noticeable drop in the enantioselectivity of the rearranged product was observed.[26] However, performing the same reaction using heterogeneous catalysis led to the formation of the product **2** with significantly higher enantioselectivity of both diastereomers (to compare, *ee* major/minor for product **2** with homogeneous catalysis – 77%/35%, heterogeneous catalysis – 86%/86%). The kinetic study of the [2,3]-Wittig rearrangement reaction of **1** with the immobilized catalyst **XXIX** revealed the full consumption of the starting material in 16 h. A decrease in *ee* of both diastereomers was also noticed, but, compared to the homogeneous catalysis, the detected drop was substantially smaller (Figure 6).

It is also worth mentioning that a simplified procedure for the isolation of the rearrangement product **2** can be applied. As a supported catalyst can be removed by filtration and the product is obtained free of any other contamination than a catalytic amount of *p*-NBA, basic extraction can be used to isolate pure product **2** in 84% yield.

In summary, different types of polystyrene-supported enantiomerically pure aminocatalysts were prepared. Among them, amino acids implemented onto the (aminomethylated)polystyrene afforded very good results in an asymmetric [2,3]-Wittig rearrangement reaction of cyclohexanone derivative **1**. The bulkiness of the end-capping moiety appeared to be critical for preserving the catalytic activity. The blocking of the unreacted primary amines of the resin with a pivaloyl group afforded immobilized catalysts that proved to be remarkably robust under the used reaction conditions, as demonstrated by recycling experiments. The catalyst **XXIX** demonstrated a high level of sustainability, as it could be recycled six times without significant deactivation. It is noteworthy that we have also shown that the isolation of the final product can be

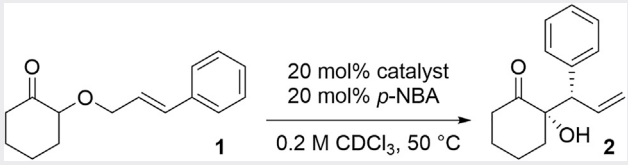
Table 2. Catalysts on (aminomethylated)polystyrene (end-capped with acetic anhydride) screening for the [2,3]-Wittig rearrangement reaction of 1



	Catalyst	Conv 16 h,%[a]	Conv 22 h,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]
1	XXIV	76	85	3.8:1	80	70
2	XXV	93	100	6:1	78	78
3	XXVI	69	82	5.1:1	92	84
4	XXVII	88	95	3.7:1	88	76
5	XXVIIIa	92	100	8.9:1	82	72

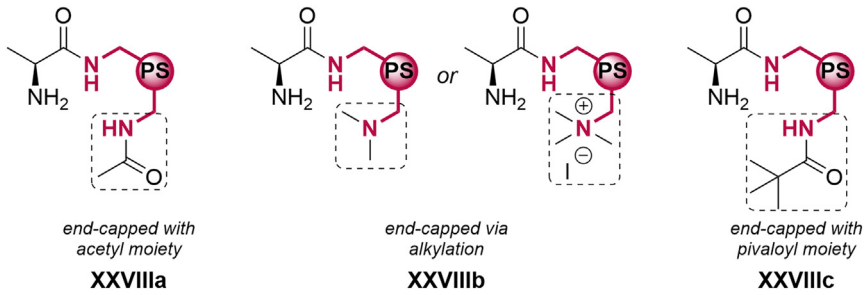
Reaction conditions: 0.1 mmol scale, catalyst (20 mol %), *p*-NBA (20 mol %), $CDCl_3$ (0.5 mL), 50°C.
[a]The conversion was determined by ^{1}H NMR of the crude reaction mixture.
[b]The diastereomeric ratio was determined by ^{1}H NMR of the crude product.
[c]The enantiomeric excess was determined by a chiral high-performance liquid chromatography (HPLC) analysis of the sample obtained by preparative thin-layer chromatography (TLC).

Table 3. Preliminary study on the recyclability of the catalysts on (aminomethylated)polystyrene



	Catalyst[a]	I Cycle	Conv 16 h,%[a]	Conv 22 h,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]	II Cycle	Conv 16 h,%[a]	Conv 22 h,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]
1	XXVIIIa		92	100	8.9:1	82	72		34	42	8.3:1	48	30
2	XXVII		88	95	3.7:1	88	76		25	31	3.7:1	56	38
3[d]	XXVIIIa		89	100	7:1	82	58		34	45	5.7:1	42	16
4[e]	XXVIIIa		84	96	6.8:1	74	46		27	35	5.9:1	25	6
5[f]	XXVIIIa		31	44	11.9:1	96	86		22	35	12.8:1	92	77
6[d,f]	XXVIIIa		29	40	9:1	94	74		19	34	7:1	88	63
7	XXVIIIb		93	100	8.6:1	87	73		60	73	8:1	70	50
8	XXVIIIc		88	100	8.6:1	86	71		91	100	8.4:1	82	65

Reaction conditions: 0.1 mmol scale, catalyst (20 mol %), *p*-NBA (20 mol %), $CDCl_3$ (0.5 mL), 50°C.
[a]The conversion was determined by ^{1}H NMR of the crude reaction mixture.
[b]The diastereomeric ratio was determined by ^{1}H NMR of the crude product.
[c]The enantiomeric excess was determined by a chiral HPLC analysis of the sample obtained by preparative TLC.
[d]Toluene was used instead of $CDCl_3$.
[e]ACN was used instead of $CDCl_3$.
[f]Reaction was conducted at 35°C.



Scheme 4. End-capping methods applied in this work

performed following a simple filtration/extraction sequence without the use of column chromatography. This simplified work-up procedure allowed us to notably reduce the isolation time, making it more suitable for up-scaling.

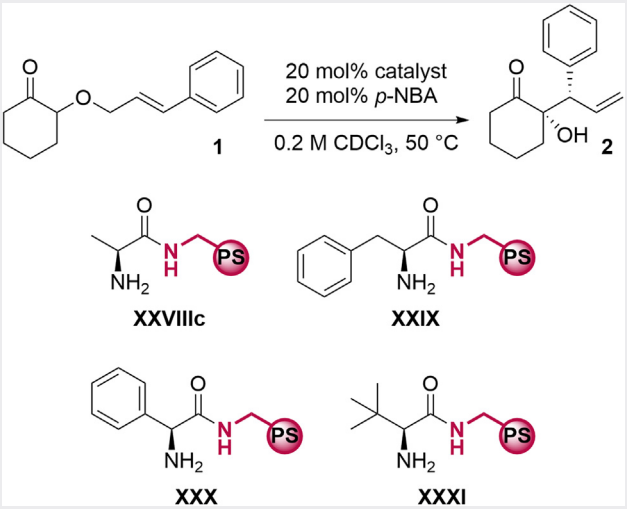
Limitations of the study

- Limitations associated with the scope of [2,3]-Wittig rearrangement of cyclohexanone derivatives can be found in our prior publication.[26]
- In this investigation, a heterogeneous catalyst with recyclability of up to six cycles is presented. Subsequent research is warranted to extend the reusability profile of the identified catalytic system.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

Table 4. Additional catalyst (end-capped by pivaloyl moiety) screening for the [2,3]-Wittig rearrangement reaction of 1



	Catalyst	Conv 16 h,%[a]	Conv 22 h,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]
1	XXVIIIc	88	100	8.6:1	86	71
2	XXIX	100	–	3.2:1	86	86
3	XXX	74	83	5:1	24	22
4	XXXI	54	65	1.8:1	37	32

Reaction conditions: 0.1 mmol scale, catalyst (20 mol %), *p*-NBA (20 mol %), $CDCl_3$ (0.5 mL), 50°C.

[a]The conversion was determined by ^{1}H NMR of the crude reaction mixture.

[b]The diastereomeric ratio was determined by ^{1}H NMR of the crude product.

[c]The enantiomeric excess was determined by a chiral high-performance liquid chromatography (HPLC) analysis of the sample obtained by preparative thin-layer chromatography (TLC).

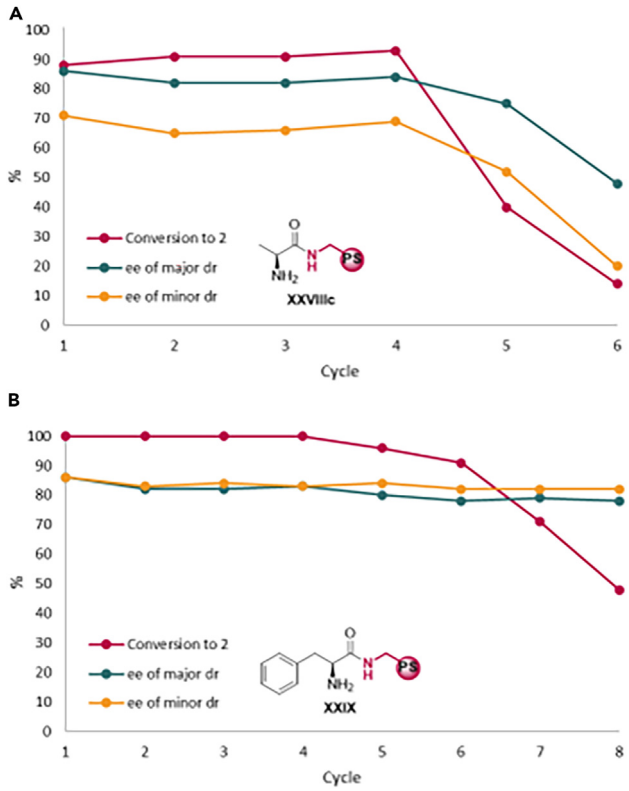


Figure 3. Recycling experiments

(A and B) Recycling experiments for the [2,3]-Wittig rearrangement reaction of 1 with catalysts **XXVIIIc** (A) and **XXIX** (B).

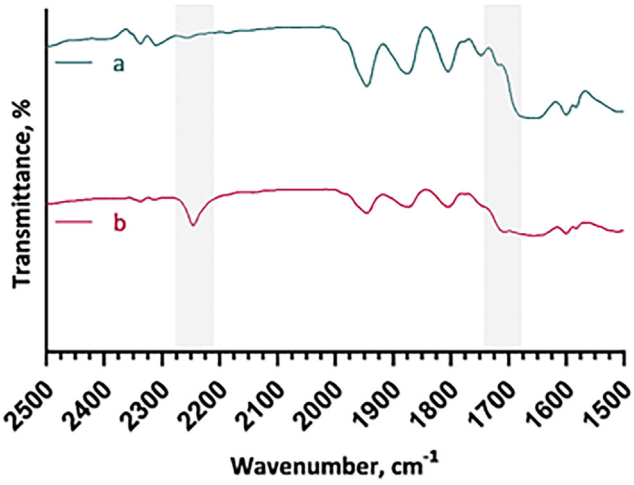


Figure 4. IR spectra

(A and B) IR spectra of freshly prepared (A) and reused (B) catalyst **XXIX**.

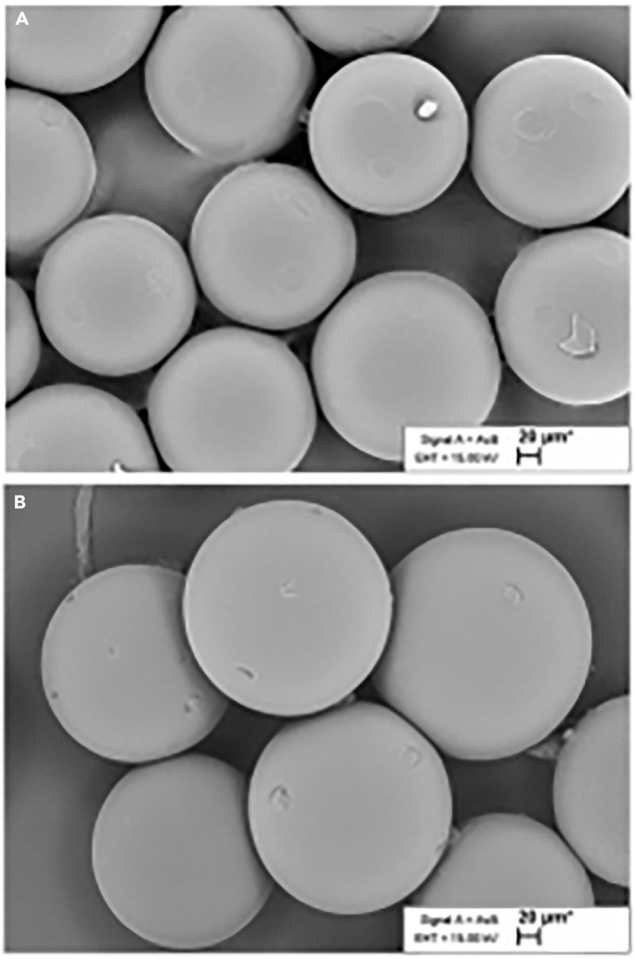


Figure 5. SEM images
(A and B) SEM images of initial (A) and deactivated (B) catalyst **XXIX**.

- Synthesis of the catalysts on the resin
- Recycling experiment

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107822.

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AUTHOR CONTRIBUTIONS

A.M. and K.E. conceived the project and conducted the synthesis. A.M. performed analysis and V.M. performed SEM analysis. All authors contributed to the discussion. A.M. and T.K. wrote the manuscript with contributions from all authors. T.K. supervised the project.

DECLARATION OF INTERESTS

The authors declare no competing interests.

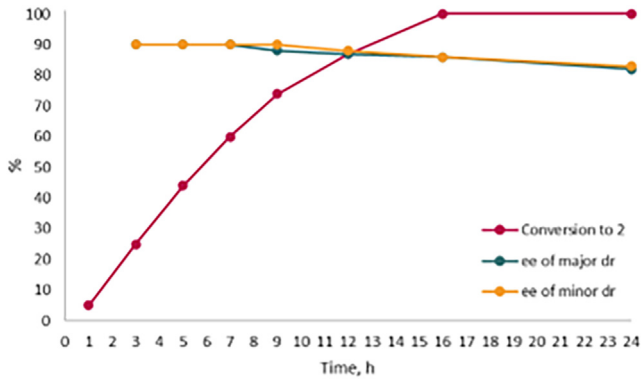

Figure 6. The reaction profile for the [2,3]-Wittig rearrangement reaction of 1 using the immobilized catalyst XXIX. The diastereoselectivity remained unchanged (3.2:1–3.3:1) during the reaction

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Deuterated chloroform	Deutero	Cas: 865-49-6
Dichloroethane	Penta	Cas: 107-06-2
Dichloromethane	Honeywell	Cas: 75-09-2
Toluene	Keemiakaubandus AS	Cas: 108-88-3
Acetonitrile	Honeywell	Cas: 75-05-8
Cyclopentyl methyl ether	Thermo Fischer Scientific	Cas: 5614-37-9
Methanol	Keemiakaubandus AS	Cas: 67-56-1
N,*N*-dimethylformamide	Thermo Fischer Scientific	Cas: 68-12-2
Isopropyl alcohol	Thermo Fischer Scientific	Cas: 67-63-0
Tetrahydrofuran	Thermo Fischer Scientific	Cas: 109-99-9
Diethyl ether	Honeywell	Cas: 60-29-7
Petroleum ether (bp: 40–60°C)	Honeywell	Cas: 8032-32-4
Ethyl acetate	Keemiakaubandus AS	Cas: 141-78-6
Hexane	Honeywell	Cas: 110-54-3
Trifluoroacetic acid	Apollo Scientific	Cas: 76-05-1
Triethylamine	Fisher Chemical	Cas: 121-44-8
Piperidine	Alfa Aesar	Cas: 110-89-4
Pyridine	Acros Organics	Cas: 110-86-1
4-dimethylaminopyridine	Acros Organics	Cas: 1122-58-3
Acetic anhydride	Reachim	Cas: 108-24-7
Para-nitrobenzoic acid	Honeywell	Cas: 62-23-7
Potassium fluoride	Sigma-Aldrich	Cas: 7789-23-3
Potassium carbonate	Lachner	Cas: 584-08-7
1-Hydroxybenzotriazole hydrate	Sigma-Aldrich	Cas: 123333-53-9
N,*N*′-diisopropylcarbodiimide	Sigma-Aldrich	Cas: 693-13-0
Triphenylphophine	Fluorochem	Cas: 603-35-0
Diisopropyl azodicarboxylate	Thermo Fisher Scientific	Cas: 2446-83-5
Diphenylphosphoryl azide	Sigma-Aldrich	Cas: 26386-88-9
Boron tribromide (1 M solution in DCM)	Sigma-Aldrich	Cas: 10294-33-4
Di-*tert*-butyl dicarbonate	Acros Organics	Cas: 24424-99-5
Iodine	Reachim	Cas: 7553-56-2
Sodium hydride (60% in mineral oil)	Sigma-Aldrich	Cas: 7646-69-7
Thionyl chloride	Acros Organics	Cas: 7719-09-7
Butyl amine	Sigma-Aldrich	Cas: 109-73-9
Pivaloyl chloride	Sigma-Aldrich	Cas: 3282-30-2
Methyl iodide	Sigma-Aldrich	Cas: 74-88-4
Boc-(L)-α-*tert*-butylglycine	Sigma-Aldrich	Cas: 62965-35-9
Boc-(L)-alanine	Orpegen	Cas: 15761-38-3
Boc-(L)-leucine	Alfa Aesar	Cas: 13139-15-6
Boc-*O*-benzyl-(L)-serine	Orpegen	Cas: 23680-31-1
Boc-(L)-methionine	Orpegen	Cas: 2488-15-5

(*Continued on next page*)

Continued

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Boc-(L)-2-propargylglycine	Sigma-Aldrich	Cas: 63039-48-5
Fmoc-(L)-phenylalanine	Sigma-Aldrich	Cas: 35661-40-6
Fmoc-(L)-isoleucine	Fluorochem	Cas: 71989-23-6
Fmoc-(L)-valine	Sigma-Aldrich	Cas: 68858-20-8
Fmoc-(L)-alanine	Orpegen	Cas: 35661-39-3
(L)-phenylalanine	Strem	Cas: 63-91-2
(L)-α-phenylglycine	Lancaster	Cas: 2935-35-5
Quinine	Sigma-Aldrich	Cas: 130-95-0
Merrifield resin LL	Sigma-Aldrich	*f* = 1.02 mmol/g, 100–200 mesh, 1% DVB
(Aminomethylated)polystyrene	Sigma-Aldrich	*f* = 1.2 mmol/g, 70–90 mesh, 1% DVB
Wang resin	Iris Biotech	*f* = 1.2 mmol/g, 100–200 mesh, 1% DVB
Software and algorithms		
ChemDraw Professional 20.0	PerkinElmer	https://www.perkinelmer.com/category/chemdraw

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Tõnis Kanger (tonis.kanger@taltech.ee).

Materials availability

All materials generated in this study are provided in the supplemental information.

IR spectra were obtained as potassium bromide pellets with a Bruker Tensor 27 FT-IR spectrophotometer. Elemental analyses were performed on Vario-Micro V2.2.0 CHNS analyzer. SEM was performed on Zeiss FEG-SEM Ultra-55. Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signals were used [$CDCl_3$ δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR), MeOD δ = 3.31 (^{1}H NMR), 49 (^{13}C NMR), and DMSO-d6 δ = 2.50 (^{1}H NMR), 39.52 (^{13}C NMR)] as internal standards. The determination of the diastereomeric ratio in the reaction mixture was based on CH_2 integrals of the double bonds (^{1}H NMR in $CDCl_3$). The internal standard (1,3,5-trimethoxybenzene) was used to check whether NMR yields are in correspondence with observed conversions. There was no difference in obtained results and only conversions were determined after that. High-resolution mass spectra were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using ESI ionization. Chiral HPLC was performed by using Chiralcel OJ-H (250 × 4.6 mm) column. Optical rotations were obtained on an Anton Paar GWB Polarimeter MCP500 in abs.EtOH and calibrated with pure solvent as a blank. Column chromatography was performed on a Biotage Isolera Prime preparative purification system with silica gel Kieselgel 40−63 μm. Precoated silica gel 60 F254 plates were used for TLC. Purchased chemicals and solvents were used as received. EtOAc was distilled over phosphorus pentoxide. Petroleum ether (PE) had a boiling point of 40–60°C. Merrifield resin LL (*f* = 1.02 mmol/g, 100–200 mesh, 1% DVB) and (aminomethylated)polystyrene (*f* = 1.2 mmol/g, 70–90 mesh, 1% DVB, N elemental analysis (%): 1.69) were purchased from Sigma-Aldrich. Wang resin (*f* = 1.2 mmol/g, 100–200 mesh, 1% DVB) was purchased from Iris Biotech. The functionalization level of each catalyst was determined by elemental analysis. The reactions were performed under air atmosphere without additional moisture elimination unless stated otherwise.

Represented work is based on our previous study of [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives, where we have used homogeneous primary amines as catalyst.[26] In this article, we provide thorough discussion about scope and limitations of the reaction.

Data and code availability

- This study does not generate new unique reagent.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper can be obtained from the lead contact upon request.

METHOD DETAILS

Synthesis of the catalysts on the resin

General procedure for the deprotection of the Boc protected catalysts (GP I)

The Boc-protected catalyst on the resin (200 mg) was swollen in DCM (2 mL) for 20 min. DCM was then removed, 50% TFA solution in DCM (2 mL) was added and the reaction mixture was shaken at rt for 5 min. After filtration, resin was suspended in the fresh batch of 50% TFA solution in DCM (2 mL). After 20 min of shaking at rt, the solid was filtered and washed successively with IPA and DCM. 10% TEA solution in DCM (2 mL) was added and the reaction mixture was shaken at rt for 10 min. After filtration, resin was suspended in the fresh batch of 10% TEA solution in DCM (2 mL). After 10 min of shaking at rt, the solid was filtered and washed successively with IPA and DCM. The solid was dried in vacuo for 24 h.

General procedure (GPII) for the preparation of the immobilized catalysts I – III

Merrifield resin (200 mg, f = 1.02 mmol/g) was suspended in 1.5 mL DMF and allowed to swell for 20 min. Boc-protected amino acid (1.5 eq) and potassium fluoride (3 eq, 36 mg) were added to the suspension and the reaction mixture was shaken at 50°C for 24 h. The solid was filtered and washed successively with DMF, DMF:H_2O (1:1), MeOH:H_2O (1:1) and MeOH. The solid was dried in vacuo for 24 h. Deprotection was performed according to the GP I.

Catalyst **I** was prepared according to the general procedure (GPII) starting from Boc-(L)-alanine (58 mg).
IR (KBr): ν 1732 cm^{-1} (carbonyl band); 1716 cm^{-1} (Boc-protecting group carbonyl band before removing).
N elemental analysis (%): 0.9, f = 0.64 mmol/g.
Catalyst **II** was prepared according to the general procedure (GPII) starting from Boc-(L)-leucine (71 mg).
IR (KBr): ν 1731 cm^{-1} (carbonyl band); 1718 cm^{-1} (Boc-protecting group carbonyl band before removing).
N elemental analysis (%): 0.82, f = 0.59 mmol/g.
Catalyst **III** was prepared according to the general procedure (GPII) starting from Boc-*O*-benzyl-(L)-serine (90 mg).
IR (KBr): ν 1736 cm^{-1} (carbonyl band); 1716 cm^{-1} (Boc-protecting group carbonyl band before removing).
N elemental analysis (%): 0.85, f = 0.61 mmol/g.

General procedure (GPIII) for the preparation of the immobilized catalysts IV – VII

Wang resin (200 mg, f = 1.2 mmol/g) was suspended in 3 mL DCM/DMF (9:1) mixture of solvents and allowed to swell for 20 min. Fmoc-protected amino acid (2 eq), HOBt (2 eq, 65 mg), *N*,*N*′-diisopropylcarbodiimide (1 eq, 38 μL), and 4-dimethylaminopyridine (0.1 eq, 3 mg) were added to the suspension and the reaction mixture was shaken at rt for 3 h. Acetic anhydride (2 eq, 45 μL) and pyridine (2 eq, 39 μL) were then added to end-cap any unreacted hydroxyl groups on the resin and the reaction mixture was shaken at rt for additional 30 min. The solid was filtered and washed successively with DMF, DCM and MeOH. The solid was dried in vacuo for 24 h. The Fmoc-protected catalyst on the resin (200 mg) was swollen in DMF (2 mL) for 20 min. DMF was then removed, 20% piperidine solution in DMF (2 mL) was added and the reaction mixture was shaken at rt for 5 min. After filtration, resin was suspended in the fresh batch of 20% piperidine solution in DMF (2 mL). After 10 min of shaking at rt, the solid was filtered and washed successively with DMF, IPA, THF, THF:MeOH (1:1) and again THF. The solid was dried in vacuo for 24 h.

Catalyst **IV** was prepared according to the general procedure (GPIII) starting from Fmoc-(L)-phenylalanine (186 mg).
IR (KBr): ν 1732, 1716 cm^{-1} (carbonyl bands), N elemental analysis (%): 0.69, f = 0.49 mmol/g.
Catalyst **V** was prepared according to the general procedure (GPIII) starting from Fmoc-(L)-isoleucine (170 mg).
IR (KBr): ν 1732, 1718 cm^{-1} (carbonyl bands), N elemental analysis (%): 0.38, f = 0.27 mmol/g.
Catalyst **VI** was prepared according to the general procedure (GPIII) starting from Fmoc-(L)-valine (163 mg).
IR (KBr): ν 1732, 1719 cm^{-1} (carbonyl bands), N elemental analysis (%): 0.42, f = 0.3 mmol/g.
Catalyst **VII** was prepared according to the general procedure (GPIII) starting from Fmoc-(L)-alanine (149 mg).
IR (KBr): ν 1732, 1716 cm^{-1} (carbonyl bands), N elemental analysis (%): 0.63, f = 0.45 mmol/g.

Synthesis of immobilized catalyst XXII

(*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine was prepared starting from quinine according to a published procedure.[34] The solution of obtained (*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine (355 mg, 1.1 mmol) in DCM (4 mL) was cooled to −78°C. Boron tribromide (5.5 mL, 5.49 mmol, 1 M solution in DCM) was added dropwise under an argon atmosphere and the mixture was allowed to warm to rt and stirred for 24 h. 1 M aq. NaOH solution was added at 0°C and the aqueous phase was extracted with DCM (3 × 10 mL). The aqueous phase was neutralized to pH 7 and was extracted with DCM (10 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the crude 4-((*S*)-amino((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) quinolin-6-ol, which was used for the next step without further purification. To a solution of 4-((*S*)-amino((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methyl)quinolin-6-ol (200 mg, 0.65 mmol) in MeOH (1.3 mL) was added di-*tert*-butyl dicarbonate (212 mg, 0.97 mmol) and iodine (16.4 mg, 0.065 mmol). The mixture was stirred at rt for 3 h. Then, sat. aq. $Na_2S_2O_3$ solution was added, and the aqueous layer was extracted with Et_2O (1 × 5 mL). The organic phase was washed with sat. aq. $NaHCO_3$ solution (1 × 5 mL), dried (Na_2SO_4), filtered and purified by column

chromatography (silica gel, 3–5% MeOH/DCM) to give the product *tert*-butyl ((*S*)-(6-hydroxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methyl)carbamate (181 mg, 68%) as an amorphous off-white solid (NMR spectra are represented in supplementary information, Figure S1).

^{1}H NMR (400 MHz, MeOD) δ 8.62 (d, *J* = 4.7 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.65 (d, *J* = 2.6 Hz, 1H), 7.51 (d, *J* = 4.7 Hz, 1H), 7.38 (dd, *J* = 9.1, 2.5 Hz, 1H), 5.93–5.75 (m, 1H), 5.53–5.31 (m, 1H), 5.15–4.96 (m, 2H), 3.67–3.45 (m, 2H), 3.45–3.32 (m, 1H), 3.04–2.81 (m, 2H), 2.59–2.34 (m, 1H), 1.87–1.63 (m, 3H), 1.62–1.47 (m, 1H), 1.37 (s, 9H), 0.98–0.83 (m, 1H).

^{13}C NMR (101 MHz, MeOD) δ 157.9, 157.5, 147.6, 144.3, 142.0, 141.4, 131.5, 130.2, 123.4, 120.8, 115.8, 105.9, 80.9, 60.9, 56.1, 52.3, 42.3, 39.9, 28.6, 28.6, 27.4, 26.3.

HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{32}N_3O_3$ 410.2438; found 410.2433.

Merrifield resin (200 mg, *f* = 1.02 mmol/g) with KI (3.4 mg, 0.02 mmol) were suspended in 4 mL DMF and allowed to swell for 20 min. *Tert*-butyl ((*S*)-(6-hydroxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)carbamate (100 mg, 0.24 mmol) and sodium hydride (12 mg, 0.31 mmol, 60% in mineral oil) were added to the suspension and the reaction mixture was shaken at 50°C for 48 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h. Deprotection was performed according to the GP I.

IR (KBr): ν 1706 cm^{-1} (Boc-protecting group carbonyl band before removal).

N elemental analysis (%): 2.54, *f* = 0.6 mmol/g.

Synthesis of the immobilized catalyst ***XXIII***

(*S*)-2-amino-*N*-butyl-3-(4-hydroxyphenyl)propenamide was prepared starting from (L)-phenylalanine according to a published procedure[35] and was used for the next step without further purification. To a solution of obtained (*S*)-2-amino-*N*-butyl-3-(4-hydroxyphenyl)propenamide (415 mg, 1.76 mmol) in MeOH (3.51 mL) was added di-*tert*-butyl dicarbonate (575 mg, 2.63 mmol) and iodine (45 mg, 0.18 mmol). The mixture was stirred at rt for 16 h. Then, sat. aq. $Na_2S_2O_3$ solution was added, and the aqueous layer was extracted with Et_2O (1 × 10 mL). The organic phase was washed with sat. aq. $NaHCO_3$ solution (1 × 10 mL), dried (Na_2SO_4), filtered and purified by column chromatography (silica gel, 3–4% MeOH/DCM) to give the product *tert*-butyl (*S*)-(1-(butylamino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (528 mg, 89%) as an off-white solid. All analytical data are in agreement with literature.[36]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.1 Hz, 2H), 6.93 (br. s, 1H), 6.77–6.71 (m, 2H), 5.91 (br. s, 1H), 5.18 (br. s, 1H), 4.21 (q, *J* = 7.3 Hz, 1H), 3.23–3.07 (m, 2H), 3.02–2.86 (m, 2H), 1.42 (s, 9H), 1.39–1.29 (m, 2H), 1.27–1.14 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

Merrifield resin (200 mg, *f* = 1.02 mmol/g) with KI (3.4 mg, 0.02 mmol) were suspended in 4 mL DMF and allowed to swell for 20 min. *Tert*-butyl (*S*)-(1-(butylamino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (82 mg, 0.24 mmol) and sodium hydride (12 mg, 0.31 mmol, 60% in mineral oil) were added to the suspension and the reaction mixture was shaken at 50°C for 48 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h. Deprotection was performed according to the GP I.

IR (KBr): ν 1671 cm^{-1} (carbonyl band); 1711 cm^{-1} (Boc-protecting group carbonyl band before removing).

N elemental analysis (%): 0.95, *f* = 0.34 mmol/g.

General procedure (GPIV) for the preparation of the immobilized catalysts ***XXIV – XXXI***

A: To a solution of corresponding amino acid (1 eq, 8.7 mmol) in MeOH (9 mL) and 1 M NaOH aq. solution (7 mL) was added di-*tert*-butyl dicarbonate (1.9 g, 8.7 mmol) and iodine (0.22 g, 0.87 mmol). The mixture was stirred at rt for 3 h. Then, sat. aq. $Na_2S_2O_3$ solution was added, and the pH was adjusted to 4 with 1 M HCl aq. solution. The aqueous layer was extracted with DCM (3 × 15 mL). The organic phase was washed with sat. aq. $NaHCO_3$ solution (1 × 15 mL), dried (Na_2SO_4), filtered and purified by column chromatography (silica gel, 10% EtOAc/PE).

Boc-(L)-α-phenylglycine was obtained according to the general procedure (GPIV-A) starting from (L)-α-phenylglycine (1.32 g) as a white solid (1.9 g, 87%). All analytical data are in agreement with literature.[37]

^{1}H NMR (400 MHz, DMSO) δ 12.77 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.46–7.25 (m, 5H), 5.11 (d, J = 8.4 Hz, 1H), 1.39 (s, 9H). $[\alpha]_D^{25}$ = 130 (*c* 0.2, abs.EtOH).

Boc-(L)-phenylalanine was prepared according to the general procedure (GPIV-A) starting from (L)-phenylalanine (1.44 g) as a white solid (2.1 g, 91%). All analytical data are in agreement with literature.[38]

^{1}H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 7.31–7.17 (m, 5H), 7.09 (d, J = 8.4 Hz, 1H), 4.09 (ddd, J = 10.3, 8.3, 4.5 Hz, 1H), 3.01 (dd, J = 13.8, 4.6 Hz, 1H), 2.82 (dd, J = 13.8, 10.3 Hz, 1H), 1.32 (s, 9H). $[\alpha]_D^{20}$ = 21 (*c* 0.17, abs.EtOH).

B: (Aminomethylated)polystyrene (500 mg, *f* = 1.2 mmol/g) was suspended in 4 mL DMF and allowed to swell for 20 min. Boc-protected amino acid (1.2 eq), HOBt (1.3 eq, 105 mg), 4-dimethylaminopyridine (0.1 eq, 7.3 mg) and *N*,*N*′-diisopropylcarbodiimide (1.2 eq, 113 μL) were added to the suspension and the reaction mixture was shaken at 60°C for 48 h. The solid was filtered, washed with DMF and directed to end-capping step. Deprotection was performed according to the GP I.

End-capping with acetic anhydride. The solid was resuspended in 4 mL DMF. Acetic anhydride (2 eq, 113 μL) and pyridine (2 eq, 97 μL) were added to the suspension and the reaction mixture was shaken at 60°C for 3 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h.

End-capping with pivaloyl chloride. The solid was resuspended in 4 mL DMF. Pivaloyl chloride (2 eq, 147 μL) and triethylamine (2 eq, 167 μL) were added to the suspension and the reaction mixture was shaken at 60°C for 3 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h.

End-capping with methyl iodide. The solid was resuspended in 4 mL DMF. Methyl iodide (4 eq, 149 μL) and potassium carbonate (2 eq, 166 mg) were added to the suspension and the reaction mixture was shaken at 60°C for 3 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h.

Catalyst **XXIV** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-(L)-methionine (180 mg).

IR (KBr) ν 1655 cm^{-1} (broad carbonyl band); 1716 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.28 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.42 mmol/g.

Catalyst **XXV** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-*O*-benzyl-(L)-serine (213 mg).

IR (KBr) ν 1655 cm^{-1} (broad carbonyl band); 1723 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.23 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.39 mmol/g.

Catalyst **XXVI** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-(L)-2-propargylglycine (154 mg).

IR (KBr) ν 1657 cm^{-1} (broad carbonyl band); 1721 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.34 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.46 mmol/g.

Catalyst **XXVII** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-(L)-leucine (167 mg).

IR (KBr) ν 1655 cm^{-1} (broad carbonyl band); 1719 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.36 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.48 mmol/g.

Catalyst **XXVIIIa** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-(L)-alanine (136 mg).

IR (KBr) ν 1652 cm^{-1} (broad carbonyl band); 1718 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.4 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.5 mmol/g.

Catalyst **XXVIIIb** was prepared according to the general procedure (GPIV-B) using end-capping with methyl iodide starting from Boc-(L)-alanine (136 mg).

IR (KBr) ν 1657 cm^{-1} (broad carbonyl band); 1720 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.5 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.58 mmol/g.

Catalyst **XXVIIIc** was prepared according to the general procedure (GPIV-B) using end-capping with pivaloyl chloride starting from Boc-(L)-alanine (136 mg).

IR (KBr) ν 1655 cm^{-1} (broad carbonyl band); 1723 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.51 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.59 mmol/g.

Catalyst **XXIX** was prepared according to the general procedure (GPIV-B) using end-capping with pivaloyl chloride starting from Boc-(L)-phenylalanine (191 mg).

IR (KBr) ν 1681 cm^{-1} (broad carbonyl band); 1716 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.23 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.39 mmol/g.

Catalyst **XXX** was prepared according to the general procedure (GPIV-B) using end-capping with pivaloyl chloride starting from Boc-(L)-α-phenylglycine (181 mg).

IR (KBr) ν 1651 cm^{-1} (broad carbonyl band); 1719 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.22 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.38 mmol/g.

Catalyst **XXXI** was prepared according to the general procedure (GPIV-B) using end-capping with pivaloyl chloride starting from Boc-(L)-α-*tert*-butylglycine (167 mg).

IR (KBr) ν 1676 cm^{-1} (broad carbonyl band); 1717 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.28 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.42 mmol/g.

[2,3]-Wittig Rearrangement Reaction of 2-(Cinnamyloxy)cyclohexan-1-one with the Polystyrene-Supported Catalyst XXIX

To a solution of 2-(cinnamyloxy)cyclohexan-1-one (0.24 mmol, 55 mg) in $CDCl_3$ (1.2 mL), catalyst **XXIX** (*f* = 0.38 mmol/g, 0.048 mmol, 126 mg) and *p-NBA* (0.048 mmol, 8 mg) were added. The reaction mixture was shaken at 50°C for 16 h. The polystyrene-supported catalyst was removed by filtration and the sat. aq. $NaHCO_3$ (5 mL) was added to the supernatant. Then, the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the product **2** (46 mg, 84%) as a white amorphous solid. All analytical data are in agreement with literature (HPLC chromatograms are represented in supplementary information, Figure S2).[26]

Major diastereomer *ee* 86% [Chiralcel OJ-H column, hexane/*i*PrOH 7:3, flow rate 1 mL/min, 35°C, λ = 210 nm; t_R (major) = 7.7 min and t_R (minor) = 11.8 min].

Minor diastereomer *ee* 86% [Chiralcel OJ-H column, hexane/*i*PrOH 7:3, flow rate 1 mL/min, 35°C, λ = 210 nm; t_R (major) = 34.6 min and t_R (minor) = 9.8 min].

Recycling experiment

To a solution of 2-(cinnamyloxy)cyclohexan-1-one in $CDCl_3$ (0.2 M), catalyst **XXVIIIc** or **XXIX** (20 mol %) and *p-NBA* (20 mol %) were added. The reaction mixture was shaken at 50°C for 16 h. The polystyrene-supported catalyst was removed by filtration and washed successively with $CHCl_3$ and MeOH. The solid was dried in vacuo for 24 h before the next portion of reactants was added. Deactivation of the catalyst could be observed by color changing as it turned brown from light yellow.